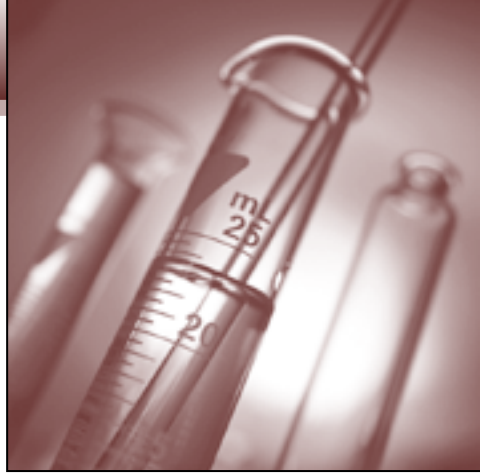

Chapter 5
ACCE Reviews of Genetic Tests: *BRCA1*, *BRCA2*, and *CFTR*

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Introduction to ACCE

ACCE is a model process for evaluating data on emerging genetic tests. It was developed by the Foundation for Blood Research through a cooperative agreement with the Centers for Disease Control and Prevention (CDC) (1). The ACCE review process builds on previously published methodologies and terminology introduced by the Secretary's Advisory Committee on Genetic Testing. The purpose of the ACCE format is to help policy makers make decisions using up-to-date and reliable information.

The acronym **ACCE** stands for the four key elements needed to evaluate any genetic test: **A**nalytic validity; **C**linical validity; **C**linical utility; and **E**thical, legal, and social implications.

- *Analytic validity* defines the ability of a test to measure the genotype of interest both accurately and reliably.
- *Clinical validity* defines the ability of a test to detect or predict the associated disorder (i.e., phenotype).
- *Clinical utility* defines the risks and benefits associated with the introduction of a test into practice. Specifically, clinical utility focuses on the health outcomes, both positive and negative, associated with testing.
- *Ethical, legal, and social implications* of the testing process include those inherent in any medical technology as well as those specific to genetic tests.

The ACCE Review Process

ACCE review differs from other evidence-based methods (e.g., those used by the U.S. Preventive Services Task Force) in that the ACCE review process is:

- Less formal (e.g., structured criteria are not always used to assess and describe the quality of the studies).

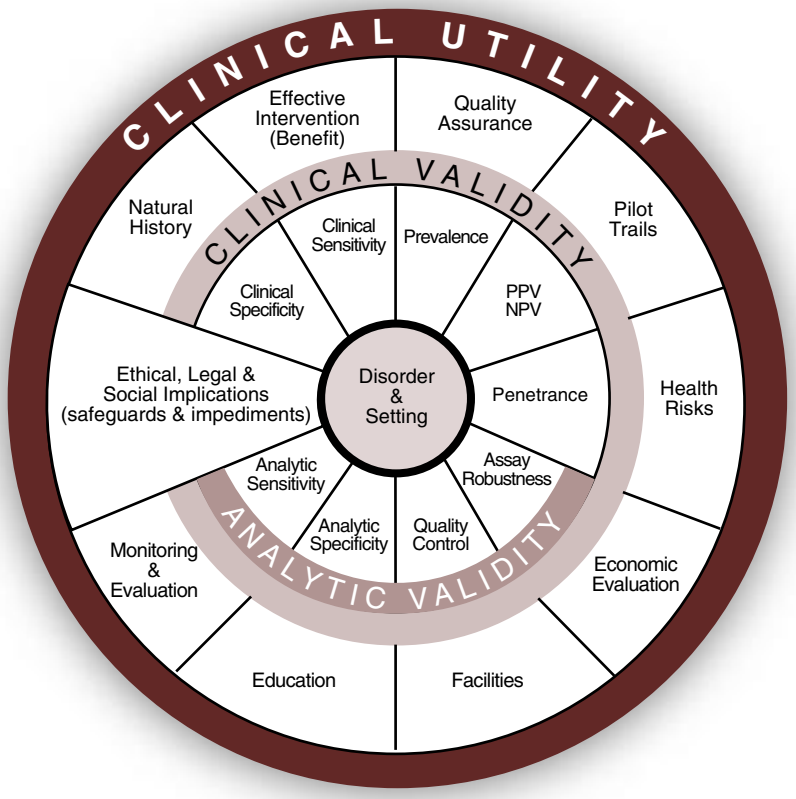
- More comprehensive (e.g., includes evaluation of assay validation and performance).
- More focused on issues associated with genetic testing.

The first step in the ACCE process is to determine the following:

- What disorder to test for, and in what setting.
- What clinical scenario to select (i.e., who is to be tested and the setting in which the testing will occur).
- What test (or tests) should be used in the clinical scenario.

The next step is an in-depth process that includes identifying, collecting, evaluating, interpreting, and reporting data about the DNA (and related) tests. A list of 44 questions forms the basis of the analytic framework. An important by-product of this process is the identification of the knowledge gaps.

The ACCE wheel, as pictured below, shows the relationships between testing components and selected topics covered within those components.



The following sections in this chapter focus on selected findings from two of the five clinical scenarios that were examined in depth as part of the *ACCE: A Model Process for Evaluating Data on Emerging Genetic Tests* project. More information is available in print form (1) as well as on the CDC website at *www.cdc.gov/genomics/gtesting/ACCE.htm*.

Family History and *BRCA1* and *BRCA2* Mutation Testing to Identify Women at Risk for Inherited Breast/Ovarian Cancer

Several professional organizations and governmental entities in the United States, Europe, and Australia recommend the routine collection of family health history pertaining to breast and ovarian cancers as a way of identifying families in which inherited forms of these cancers may exist (2-4).

The ACCE project reviewed the ability of family health histories and subsequent *BRCA1* and *BRCA2* mutation testing to help prevent breast and ovarian cancers. In addition, both were then examined for their potential from a public health perspective. One important result of this review was the insight gained on how to integrate important parameters commonly provided to patients/public health professionals into one consistent, interrelated framework that could be used to refine published estimates (5). Example 1 shows estimates based on epidemiologic data commonly provided to patients or public health professionals.

Example 1. Estimates of Epidemiological Data Commonly Given to Patients/Public Health Professionals

Cumulative incidence of cancer is often provided for a specific age (e.g., by age 70) and is the proportion of women within a given population that is expected to develop breast cancer by that age. **Approximately 1 in 10 women will develop breast cancer by age 70 (6).**

Mutation prevalence is a measure of how often mutations in the *BRCA1* or *BRCA2* gene occur in an unselected group of women. Only a few studies have addressed mutation prevalence for these genes and have done so indirectly. **Approximately 1 in 300 to 1 in 450 women have a mutation in the *BRCA1* or *BRCA2* gene.**

Clinical sensitivity is the proportion of women with a *BRCA1* or *BRCA2* mutation among breast cancer cases. Because most breast cancer cases are sporadic, estimated clinical sensitivity is low. **Reports range widely from 2% to 10% of breast cancer cases by age 70.**

Penetrance is defined as the proportion of women with a mutation in the *BRCA1* or *BRCA2* gene that will develop breast cancer by a given age. **Published penetrance estimates vary from 35% to 80% by age 70.**

In general, most published studies have focused on only one or two of these parameters simultaneously; however, more reliable results for each can be computed if they are considered together and integrated into one consistent, interrelated framework.

Example 2 shows internally derived, consistent values for four of these interrelated parameters (5). The "reasonable ranges" are less broad than the range of estimates contained in the published literature (*see Example 1*), particularly for clinical sensitivity and penetrance.

Example 2. Internally Consistent Estimates of Epidemiological Data

- *Cumulative incidence* of breast cancer by age 70: 9.7% (approximately 1 in 10 women).
- *Mutation prevalence* for *BRCA1* and *BRCA2* in the general population: 1:380 (reasonable range: 1:310 to 1:465).
- *Clinical sensitivity* of *BRCA1* and *BRCA2* mutations and breast cancer by age 70: 1.5% (reasonable range: 1.0% to 2.0%).
- *Penetrance* of the two mutations by age 70: 55% (reasonable range: 35% to 65%).

Other important findings of the ACCE review for family health history and *BRCA1* and *BRCA2* mutation testing include the following:

- Some common sources for information about mutation testing and breast cancer provide information that is not consistent with the current literature.
- The current protocols for interpreting family histories for breast and ovarian cancers are not strictly evidence-based; they do not agree on what constitutes evidence of an inherited form of breast/ovarian cancer (7) and are likely to identify some women as screening positive whose probability of having a mutation is relatively low (8).
- Significant gaps in knowledge exist for estimating the analytic validity and clinical validity of *BRCA1* and *BRCA2* mutation testing. The reason for these gaps in knowledge is mainly due to the expense of full sequencing and the limitations imposed on both genes by the patents held by Myriad Genetic Laboratories, Inc.*

** Use of trade names is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.*

Programs that provide information to health professionals or patients about the epidemiology of breast cancer and *BRCA1* and *BRCA2* mutation testing might consider reviewing their materials in order to determine whether updates are warranted. In addition, any group considering implementing a family health history screening protocol in the general population (e.g., in primary care) should carefully evaluate the performance of the screening protocol prior to its widespread introduction. *For more information on Family History, see Chapter 2, CDC's Family History Public Health Initiative: 2005 Update.*

Preconception and Prenatal Screening for Cystic Fibrosis via *CFTR* Carrier Testing

During 1997, a National Institutes of Health consensus conference recommended offering cystic fibrosis transmembrane conductance regulator (*CFTR*) carrier testing to pregnant couples and couples planning to become pregnant (9). Soon after this recommendation was made, the American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG) were charged with overseeing the implementation of *CFTR* carrier testing. They produced recommendations that include the panel of mutations to be tested and patient educational materials (10,11). A full ACCE review was performed after these policies were introduced in 2001. For more information, visit the website: *http://www.cdc.gov/genomics/activities/ogdp/2003/chap09.htm*.

Results of the ACCE review were used by ACMG to update Laboratory Standards and Guidelines in 2004 (12). Selected new or important findings from the ACCE review include the following:

- Previously unpublished evidence showed for the first time that *CFTR* mutation testing is highly reliable. Analytic sensitivity (i.e., the proportion of samples with a *CFTR* mutation that was correctly identified) was approximately 98%, whereas analytic specificity (i.e., the proportion of samples without a correctly identified *CFTR* mutation) was approximately 99.7% (13).

- Clinical sensitivity (i.e., the proportion of carrier couples that could be identified by the ACMG-recommended panel of mutations) was estimated for broad racial/ethnic categories (e.g., 78% of non-Hispanic Caucasian carrier couples, 42% of African American carrier couples).

- The prevalence of "classic" cystic fibrosis (CF) was estimated for the same racial/ethnic categories (e.g., 1:2,500 for non-Hispanic Caucasian couples, 1:15,100 for African American couples).

- Methods and data are lacking to evaluate the impact of preconception and prenatal screening for CF. Current regulations (e.g., Health Insurance Portability and Accountability Act of 1996, or HIPAA) and health care reimbursement issues complicate the collection of key information (e.g., specific risks and benefits, acceptability, and cost-effectiveness) (14).

Health care providers interpreting *CFTR* mutation test results as part of preconception or prenatal carrier screening for CF should review the revised laboratory standards and guidelines for updated information. The ACCE review helps to clarify issues related to the offering of this testing to members of different racial/ethnic groups. Because of the low prevalence and poor clinical sensitivity of some of these group populations, the resources required to detect each carrier could be more than 40 times greater than in other racial/ethnic groups.

Lessons Learned

The ACCE project has provided the following lessons:

- Comprehensive evidence-based reports, such as an ACCE review, are expensive, are labor intensive, and require multiple areas of expertise. Final reports are often cumbersome to review and digest. These reviews, therefore, are best undertaken by a group that has experience in extracting and summarizing data from the literature with guidance from content experts.

- Overall, the benefit of a structured, systematic approach to evidence collection and evaluation for any given topic must be balanced against the urgency of need for such an investment of time and effort. At present, only a limited number of genetic tests are likely to have sufficiently broad applications and available data to justify such an effort. The ACCE process was designed specifically to produce an evidence base for policy decisions while refraining from making recommendations.

These and other issues concerning evidence-based reviews of genetic testing are being addressed by a new CDC initiative entitled Evaluation of Genomic Applications in Practice and Prevention (EGAPP). *For more information on this initiative, see Chapter 6, Evaluation of Genomic Applications in Practice and Prevention: Implementation and Evaluation of a Model Approach.*

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